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  * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 12:50:08 ON 13 JUN 2005

=> fil .bec
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         0.21       0.21

FILES 'MEDLINE, SCISEARCH, LIFESCI, BIOTECHDS, BIOSIS, EMBASE, HCAPLUS, NTIS,
       ESBIOBASE, BIOTECHNO, WPIDS' ENTERED AT 12:50:19 ON 13 JUN 2005
ALL COPYRIGHTS AND RESTRICTIONS APPLY.  SEE HELP USAGETERMS FOR DETAILS.

11 FILES IN THE FILE LIST

=> s src(5a)(family or member#)(5a)redundanc?
FILE 'MEDLINE'
         15564 SRC
        410717 FAMILY
        158241 MEMBER#
          4157 REDUNDANC?
L1           4 SRC(5A)(FAMILY OR MEMBER#)(5A)REDUNDANC?

FILE 'SCISEARCH'
         14911 SRC
        296430 FAMILY
        159315 MEMBER#
          9712 REDUNDANC?
L2           4 SRC(5A)(FAMILY OR MEMBER#)(5A)REDUNDANC?

FILE 'LIFESCI'
          5735 SRC
         87715 FAMILY
         61599 MEMBER#
          1814 REDUNDANC?
L3           2 SRC(5A)(FAMILY OR MEMBER#)(5A)REDUNDANC?

FILE 'BIOTECHDS'
           306 SRC
          6405 FAMILY
          5460 MEMBER#
           248 REDUNDANC?
L4           1 SRC(5A)(FAMILY OR MEMBER#)(5A)REDUNDANC?

FILE 'BIOSIS'
         14939 SRC
        266795 FAMILY
        150656 MEMBER#
          4178 REDUNDANC?
L5           4 SRC(5A)(FAMILY OR MEMBER#)(5A)REDUNDANC?

FILE 'EMBASE'
         11510 SRC
        276052 FAMILY
        135035 MEMBER#
          3521 REDUNDANC?
L6           4 SRC(5A)(FAMILY OR MEMBER#)(5A)REDUNDANC?

FILE 'HCAPLUS'
         15384 SRC
        192731 FAMILY
        187790 MEMBER#
          4586 REDUNDANC?
L7           6 SRC(5A)(FAMILY OR MEMBER#)(5A)REDUNDANC?
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FILE 'NTIS'
          2025 SRC
         20118 FAMILY
         34890 MEMBER#
          2899 REDUNDANC?
L8           0 SRC(5A)(FAMILY OR MEMBER#)(5A)REDUNDANC?

FILE 'ESBIOBASE'
          7976 SRC
        112813 FAMILY
         73640 MEMBER#
          2514 REDUNDANC?
L9           4 SRC(5A)(FAMILY OR MEMBER#)(5A)REDUNDANC?

FILE 'BIOTECHNO'
          7046 SRC
         96325 FAMILY
         58040 MEMBER#
          1383 REDUNDANC?
L10          2 SRC(5A)(FAMILY OR MEMBER#)(5A)REDUNDANC?

FILE 'WPIDS'
           950 SRC
         12745 FAMILY
        668007 MEMBER#
          8913 REDUNDANC?
L11          0 SRC(5A)(FAMILY OR MEMBER#)(5A)REDUNDANC?

TOTAL FOR ALL FILES
L12         31 SRC(5A)(FAMILY OR MEMBER#)(5A) REDUNDANC?

=> dup rem l12
PROCESSING COMPLETED FOR L12
L13           6 DUP REM L12 (25 DUPLICATES REMOVED)

=> d tot

L13  ANSWER 1 OF 6     MEDLINE on STN                    DUPLICATE 1
TI   Molecular mechanism for the potentiation of the transcriptional activity
     of human liver receptor homolog 1 by steroid receptor coactivator-1.
SO   Molecular endocrinology (Baltimore, Md.), (2004 Aug) 18 (8) 1887-905.
     Electronic Publication: 2004-05-13.
     Journal code: 8801431. ISSN: 0888-8809.
AU   Xu Ping-Long; Liu Yun-Qing; Shan Shi-Fang; Kong Yu-Ying; Zhou Qing; Li
     Mei; Ding Jian-Ping; Xie You-Hua; Wang Yuan
AN   2004374296     MEDLINE

L13  ANSWER 2 OF 6     MEDLINE on STN                    DUPLICATE 2
TI   Review of the in vivo functions of the p160 steroid receptor coactivator
     family.
SO   Molecular endocrinology (Baltimore, Md.), (2003 Sep) 17 (9) 1681-92.
     Electronic Publication: 2003-06-12. Ref: 88
     Journal code: 8801431. ISSN: 0888-8809.
AU   Xu Jianming; Li Qingtian
AN   2003400993     MEDLINE

L13  ANSWER 3 OF 6     MEDLINE on STN                    DUPLICATE 3
TI   Production of mouse ES cells homozygous for Cdk5-phosphorylated site
     mutation in c-Src alleles.
SO   Journal of biochemistry, (2003 May) 133 (5) 563-9.
     Journal code: 0376600. ISSN: 0021-924X.
AU   Kato Goro; Maeda Shuichiro
AN   2003275354     MEDLINE
```

L13 ANSWER 4 OF 6 HCAPLUS COPYRIGHT 2005 ACS on STN
TI The role of Src family tyrosine kinase in T cell signal transduction
SO Ensho to Men'eki (2002), Volume Date 2003, 11(1), 90-98
CODEN: ENMEFA; ISSN: 0918-8371
AU Suzuki, Takeshi
AN 2003:49575 HCAPLUS
DN 138:88160

L13 ANSWER 5 OF 6 MEDLINE on STN DUPLICATE 4
TI Requirement for Src family protein tyrosine kinases in G2 for fibroblast cell division.
SO Science, (1995 Sep 15) 269 (5230) 1567-9.
Journal code: 0404511. ISSN: 0036-8075.
AU Roche S; Fumagalli S; Courtneidge S A
AN 95397147 MEDLINE

L13 ANSWER 6 OF 6 HCAPLUS COPYRIGHT 2005 ACS on STN
TI Transgenic mice with non-receptor type protein tyrosine kinase
SO Molecular Medicine (Tokyo) (1994), (Suppl. 421), 273-8
CODEN: MOLMEL; ISSN: 0918-6557
AU Aizawa, Shinichi
AN 1995:336250 HCAPLUS
DN 122:129742

=> d ab 1-6

L13 ANSWER 1 OF 6 MEDLINE on STN DUPLICATE 1
AB The liver receptor homolog 1 (LRH-1) belongs to the Fushi tarazu factor 1 nuclear receptor subfamily, and its biological functions are just being unveiled. The molecular mechanism for the transcriptional regulation by LRH-1 is not clear yet. In this report, we use mutagenesis and reporter gene assays to carry out a detailed analysis on the hinge region and the proximal ligand binding domain (LBD) of human (h) LRH-1 that possess important regulatory functions. Our results indicate that helix 1 of the LBD is essential for the activity of hLRH-1 and that the steroid receptor coactivator (SRC)-1 interacts directly with the LBD of hLRH-1 and significantly potentiates the transcriptional activity of hLRH-1. Cotransfection assays demonstrate that overexpressed SRC-1 potentiates hLRH-1 mediated activation of the cholesterol 7-alpha-hydroxylase promoter and increases the transcription of the endogenous cholesterol 7-alpha-hydroxylase in Huh7 cells. The interaction between SRC-1 and hLRH-1 assumes a unique pattern that involves primarily a region containing the glutamine-rich domain of SRC-1, and helix 1 and activation function-2 of hLRH-1 LBD. Mutagenesis and molecular modeling studies indicate that, similar to mouse LRH-1, the coactivator-binding cleft of hLRH-1 LBD is not optimized. An interaction between helix 1 of hLRH-1 LBD and a region containing the glutamine-rich domain of SRC-1 can provide an additional stabilizing force and enhances the recruitment of SRC-1. Similar interaction is observed between hLRH-1 and SRC-2/transcriptional intermediary factor 2 or SRC-3/acetyltransferase. Moreover, transcriptional intermediary factor 2 and acetyltransferase also potentiate the transcriptional activity of hLRH-1, suggesting a functional **redundancy** among **SRC family members.** These findings collectively demonstrate an important functional role of helix 1 in cofactor recruitment and reveal a novel molecular mechanism of transcriptional regulation and cofactor recruitment mediated by hLRH-1.

L13 ANSWER 2 OF 6 MEDLINE on STN DUPLICATE 2
AB The p160 steroid receptor coactivator (SRC) gene family contains three homologous members, which serve as transcriptional coactivators for nuclear receptors and certain other transcription factors. These coactivators interact with ligand-bound nuclear receptors to recruit

histone acetyltransferases and methyltransferases to specific enhancer/promotor regions, which facilitates chromatin remodeling, assembly of general transcription factors, and transcription of target genes. This minireview summarizes our current knowledge about the molecular structures, molecular mechanisms, temporal and spatial expression patterns, and biological functions of the SRC family. In particular, this article highlights the roles of SRC-1 (NCoA-1), SRC-2 (GRIP1, TIF2, or NCoA-2) and SRC-3 (p/CIP, RAC3, ACTR, AIB1, or TRAM-1) in development, organ function, endocrine regulation, and nuclear receptor function, which are defined by characterization of the genetically manipulated animal models. Furthermore, this article also reviews our current understanding of the role of SRC-3 in breast cancer and discusses possible mechanisms for functional specificity and **redundancy** among **SRC family members.**

L13 ANSWER 3 OF 6 MEDLINE on STN DUPLICATE 3
AB c-Src-null mutants have not provided a full understanding of the cellular functions of c-Src, reflecting the functional **redundancy** among **Src family members.** c-**Src** is phosphorylated by cyclin-dependent kinase 1 (Cdk1) and Cdk5 at Ser75 in the unique amino terminal c-Src-specific domain. The specific roles of c-Src may be assessed by establishing mouse embryonic stem (ES) cells homozygous for a point mutation at Ser75. Mammalian homozygous cultured cells with a point mutation, however, have not yet been produced by gene targeting. Here we show an efficient procedure for producing ES cell clones bearing a homozygous Ser75 to Asp mutation in the c-src gene. This procedure was developed by combining two previously reported strategies: our procedure for introducing a point mutation into one allele with no exogenous sequence, and the high-geneticin (G418) selection procedure for introducing a mutation into both alleles. The mutant clones expressed the same levels of c-Src protein and autophosphorylation activity as wild-type cells, but the mutant c-Src was not phosphorylated on Ser75 during mitosis. This procedure is feasible for generating cells homozygous for a subtle mutation in most genes, and is expected to be applicable to other somatic cell lines.

L13 ANSWER 4 OF 6 HCAPLUS COPYRIGHT 2005 ACS on STN
AB A review on **redundancy** and specificity of **Src family** kinase including Lck and Fyn, structure and regulatory mechanism of Src family kinase, Lck activity equilibrium in the resting T cells, Lck activation and ITAM phosphorylation after TCR crosslinking, Lck activity keeping after TCR crosslinking and immune synapse, and involvement of Fyn in T cell signaling.

L13 ANSWER 5 OF 6 MEDLINE on STN DUPLICATE 4
AB The protein tyrosine kinase c-Src is transiently activated at the transition from the G2 phase to mitosis in the cell cycle of mammalian fibroblasts. Fyn and Yes, the other members of the Src family present in fibroblasts, were also found to be activated at mitosis. In cells microinjected with a neutralizing antibody specific for Src, Fyn, and Yes (anti-cst.1) during G2, cell division was inhibited by 75 percent. The block occurred before nuclear envelope breakdown. Antibodies specific for phosphatidylinositol-3 kinase alpha and phospholipase C-gamma 1 had no effect. Microinjection of the Src homology 2 (SH2) domain of Fyn was also inhibitory. Functional **redundancy** between **members** of the **Src family** was observed; a **Src**-specific antibody had no effect in NIH 3T3 cells but inhibited cell division in fibroblasts in which the only functional Src family kinase was Src itself. Thus, Src family kinases and proteins associating with their SH2 domains are required for entry into mitosis.

L13 ANSWER 6 OF 6 HCAPLUS COPYRIGHT 2005 ACS on STN
AB A review, with 23 refs., on the effects in knock out mice of the **Src family** kinase possibly due to gene

redundancy. Csk gene knock out in mice is lethal during pregnancy at day 8.5 from gestation by death of nerve epithelial cells and moving nerve crown cells. Fak gene knock out in mice is lethal at 8 days of gestation by anomaly in mesoderm possibly due to deletion of signal transduction of fibronectin-integrin interaction. Knock out mice for abl, srm, or Btk are discussed.

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=> log y
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                    23.23      23.44

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                       ENTRY    SESSION
CA SUBSCRIBER PRICE                                    -1.46      -1.46

STN INTERNATIONAL LOGOFF AT 12:55:22 ON 13 JUN 2005


  * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 12:56:31 ON 13 JUN 2005

=> fil .bec
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     0.21       0.21

FILES 'MEDLINE, SCISEARCH, LIFESCI, BIOTECHDS, BIOSIS, EMBASE, HCAPLUS, NTIS,
       ESBIOBASE, BIOTECHNO, WPIDS' ENTERED AT 12:56:40 ON 13 JUN 2005
ALL COPYRIGHTS AND RESTRICTIONS APPLY.  SEE HELP USAGETERMS FOR DETAILS.

11 FILES IN THE FILE LIST

=> s function?(4a)redundan?
FILE 'MEDLINE'
       1349310 FUNCTION?
         10396 REDUNDAN?
L1        1825 FUNCTION?(4A)REDUNDAN?

FILE 'SCISEARCH'
       1696895 FUNCTION?
         19709 REDUNDAN?
L2        2096 FUNCTION?(4A)REDUNDAN?

FILE 'LIFESCI'
        335638 FUNCTION?
          4274 REDUNDAN?
L3        1151 FUNCTION?(4A)REDUNDAN?

FILE 'BIOTECHDS'
         36904 FUNCTION?
           575 REDUNDAN?
L4           23 FUNCTION?(4A)REDUNDAN?

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       1265037 FUNCTION?
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L5        1799 FUNCTION?(4A)REDUNDAN?

FILE 'EMBASE'
       1281478 FUNCTION?
          8941 REDUNDAN?
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L6          1580 FUNCTION?(4A)REDUNDAN?

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         2054507 FUNCTION?
           11046 REDUNDAN?
L7          1902 FUNCTION?(4A)REDUNDAN?

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          215297 FUNCTION?
            5098 REDUNDAN?
L8           116 FUNCTION?(4A)REDUNDAN?

FILE 'ESBIOBASE'
          513942 FUNCTION?
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L9          1515 FUNCTION?(4A)REDUNDAN?

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          299708 FUNCTION?
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FILE 'WPIDS'
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           20114 REDUNDAN?
L11          502 FUNCTION?(4A)REDUNDAN?

TOTAL FOR ALL FILES
L12        13516 FUNCTION?(4A) REDUNDAN?

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FILE 'MEDLINE'
           15564 SRC
          236428 KINASE#
          410717 FAMILY
L13         6629 SRC(3A)(KINASE# OR FAMILY)

FILE 'SCISEARCH'
           14911 SRC
          265282 KINASE#
          296430 FAMILY
L14         6512 SRC(3A)(KINASE# OR FAMILY)

FILE 'LIFESCI'
            5735 SRC
           72861 KINASE#
           87715 FAMILY
L15         2581 SRC(3A)(KINASE# OR FAMILY)

FILE 'BIOTECHDS'
             306 SRC
            8831 KINASE#
            6405 FAMILY
L16           84 SRC(3A)(KINASE# OR FAMILY)

FILE 'BIOSIS'
           14939 SRC
          283542 KINASE#
          266795 FAMILY
L17         6796 SRC(3A)(KINASE# OR FAMILY)

FILE 'EMBASE'
           11510 SRC
          207930 KINASE#
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        276052 FAMILY
L18       5217 SRC(3A)(KINASE# OR FAMILY)

FILE 'HCAPLUS'
         15384 SRC
        248736 KINASE#
        192731 FAMILY
L19       7533 SRC(3A)(KINASE# OR FAMILY)

FILE 'NTIS'
          2025 SRC
          1664 KINASE#
         20118 FAMILY
L20         98 SRC(3A)(KINASE# OR FAMILY)

FILE 'ESBIOBASE'
          7976 SRC
        113475 KINASE#
        112813 FAMILY
L21       3994 SRC(3A)(KINASE# OR FAMILY)

FILE 'BIOTECHNO'
          7046 SRC
         92256 KINASE#
         96325 FAMILY
L22       2978 SRC(3A)(KINASE# OR FAMILY)

FILE 'WPIDS'
           950 SRC
         11065 KINASE#
         12745 FAMILY
L23        258 SRC(3A)(KINASE# OR FAMILY)

TOTAL FOR ALL FILES
L24      42680 SRC(3A)(KINASE# OR FAMILY)

=> s l12 and l24
FILE 'MEDLINE'
L25         25 L1 AND L13

FILE 'SCISEARCH'
L26         24 L2 AND L14

FILE 'LIFESCI'
L27         14 L3 AND L15

FILE 'BIOTECHDS'
L28          1 L4 AND L16

FILE 'BIOSIS'
L29         21 L5 AND L17

FILE 'EMBASE'
L30         21 L6 AND L18

FILE 'HCAPLUS'
L31         22 L7 AND L19

FILE 'NTIS'
L32          0 L8 AND L20

FILE 'ESBIOBASE'
L33         18 L9 AND L21
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FILE 'BIOTECHNO'
L34 11 L10 AND L22

FILE 'WPIDS'
L35 0 L11 AND L23

TOTAL FOR ALL FILES
L36 157 L12 AND L24

=> dup rem 136
PROCESSING COMPLETED FOR L36
L37 33 DUP REM L36 (124 DUPLICATES REMOVED)

=> d tot

L37 ANSWER 1 OF 33 MEDLINE on STN DUPLICATE 1
TI Dynamic Regulation of Tec Kinase Localization in Membrane-proximal Vesicles of a T Cell Clone Revealed by Total Internal Reflection Fluorescence and Confocal Microscopy.
SO Journal of biological chemistry, (2005 Jun 10) 280 (23) 21949-54. Electronic Publication: 2005-04-06. Journal code: 2985121R. ISSN: 0021-9258.
AU Kane Lawrence P; Watkins Simon C
AN 2005290968 IN-PROCESS

L37 ANSWER 2 OF 33 HCAPLUS COPYRIGHT 2005 ACS on STN
TI The non-transmembrane form of Delta1, but not of Jagged1, induces normal migratory behavior accompanied by fibroblast growth factor receptor 1-dependent transformation
SO Journal of Biological Chemistry (2004), 279(14), 13285-13288 CODEN: JBCHA3; ISSN: 0021-9258
AU Trifonova, Radiana; Small, Deena; Kacer, Doreen; Kovalenko, Dmitry; Kolev, Vihren; Mandinova, Anna; Soldi, Raffaella; Liaw, Lucy; Prudovsky, Igor; Maciag, Thomas
AN 2004:263562 HCAPLUS
DN 140:400410

L37 ANSWER 3 OF 33 MEDLINE on STN DUPLICATE 2
TI **Src-family kinases** in B-cell development and signaling.
SO Oncogene, (2004 Oct 18) 23 (48) 8001-6. Ref: 70 Journal code: 8711562. ISSN: 0950-9232.
AU Gauld Stephen B; Cambier John C
AN 2004519147 MEDLINE

L37 ANSWER 4 OF 33 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN
TI Enteropathogenic Escherichia coli use redundant tyrosine kinases to form actin pedestals
SO MOLECULAR BIOLOGY OF THE CELL, (AUG 2004) Vol. 15, No. 8, pp. 3520-3529. Publisher: AMER SOC CELL BIOLOGY, 8120 WOODMONT AVE, STE 750, BETHESDA, MD 20814-2755 USA. ISSN: 1059-1524.
AU Swimm A; Bommarius B; Li Y; Cheng D; Reeves P; Sherman M; Veach D; Bornmann W; Kalman D (Reprint)
AN 2004:705761 SCISEARCH

L37 ANSWER 5 OF 33 MEDLINE on STN DUPLICATE 3
TI Molecular mechanism for the potentiation of the transcriptional activity of human liver receptor homolog 1 by steroid receptor coactivator-1.
SO Molecular endocrinology (Baltimore, Md.), (2004 Aug) 18 (8) 1887-905. Electronic Publication: 2004-05-13. Journal code: 8801431. ISSN: 0888-8809.
AU Xu Ping-Long; Liu Yun-Qing; Shan Shi-Fang; Kong Yu-Ying; Zhou Qing; Li

Mei; Ding Jian-Ping; Xie You-Hua; Wang Yuan
AN 2004374296 MEDLINE

L37 ANSWER 6 OF 33 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN
TI Lipid rafts: resolution of the 'fyn problem"?
SO MOLECULAR IMMUNOLOGY, (JUL 2004) Vol. 41, No. 6-7, pp. 645-656.
Publisher: PERGAMON-ELSEVIER SCIENCE LTD, THE BOULEVARD, LANGFORD LANE, KIDLINGTON, OXFORD OX5 1GB, ENGLAND.
ISSN: 0161-5890.
AU Filipp D; Julius M (Reprint)
AN 2004:705869 SCISEARCH

L37 ANSWER 7 OF 33 MEDLINE on STN DUPLICATE 4
TI Review of the in vivo functions of the p160 steroid receptor coactivator family.
SO Molecular endocrinology (Baltimore, Md.), (2003 Sep) 17 (9) 1681-92.
Electronic Publication: 2003-06-12. Ref: 88
Journal code: 8801431. ISSN: 0888-8809.
AU Xu Jianming; Li Qingtian
AN 2003400993 MEDLINE

L37 ANSWER 8 OF 33 MEDLINE on STN DUPLICATE 5
TI Production of mouse ES cells homozygous for Cdk5-phosphorylated site mutation in c-Src alleles.
SO Journal of biochemistry, (2003 May) 133 (5) 563-9.
Journal code: 0376600. ISSN: 0021-924X.
AU Kato Goro; Maeda Shuichiro
AN 2003275354 MEDLINE

L37 ANSWER 9 OF 33 MEDLINE on STN DUPLICATE 6
TI SRC-1 null mice exhibit moderate motor dysfunction and delayed development of cerebellar Purkinje cells.
SO Journal of neuroscience : official journal of the Society for Neuroscience, (2003 Jan 1) 23 (1) 213-22.
Journal code: 8102140. ISSN: 1529-2401.
AU Nishihara Eijun; Yoshida-Komiya Hiromi; Chan Chi-Shing; Liao Lan; Davis Ronald L; O'Malley Bert W; Xu Jianming
AN 2003007952 MEDLINE

L37 ANSWER 10 OF 33 MEDLINE on STN DUPLICATE 7
TI Constitutive activation of the **SRC family kinase** Hck results in spontaneous pulmonary inflammation and an enhanced innate immune response.
SO Journal of experimental medicine, (2002 Sep 2) 196 (5) 589-604.
Journal code: 2985109R. ISSN: 0022-1007.
AU Ernst Matthias; Inglese Melissa; Scholz Glen M; Harder Kenneth W; Clay Fiona J; Bozinovski Steven; Waring Paul; Darwiche Rima; Kay Tom; Sly Peter; Collins Rachel; Turner Debra; Hibbs Margaret L; Anderson Gary P; Dunn Ashley R
AN 2002471842 MEDLINE

L37 ANSWER 11 OF 33 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
TI Functional and biochemical consequences of abrogating the activation of diverse signaling pathways in c-Kit: Restoration of Src signaling pathway in c-Kit alone is sufficient to partially restore cooperation with Epo-R.
SO Blood, (November 16, 2001) Vol. 98, No. 11 Part 1, pp. 75a-76a. print.
Meeting Info.: 43rd Annual Meeting of the American Society of Hematology, Part 1. Orlando, Florida, USA. December 07-11, 2001. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
AU Tan, Bai Lin [Reprint author]; Hong, Li [Reprint author]; Kapur, Reuben [Reprint author]

AN 2002:129751 BIOSIS

L37 ANSWER 12 OF 33 MEDLINE on STN DUPLICATE 8
TI Mesoderm-independent regulation of gastrulation movements by the **src** tyrosine **kinase** in Xenopus embryo.
SO Differentiation; research in biological diversity, (2001 Dec) 69 (1) 38-48.
Journal code: 0401650. ISSN: 0301-4681.
AU Denoyelle M; Valles A M; Lentz D; Thiery J P; Boyer B
AN 2002048749 MEDLINE

L37 ANSWER 13 OF 33 MEDLINE on STN DUPLICATE 9
TI The B-cell-specific **Src-family kinase** Blk is dispensable for B-cell development and activation.
SO Molecular and cellular biology, (2000 Feb) 20 (4) 1227-33.
Journal code: 8109087. ISSN: 0270-7306.
AU Texido G; Su I H; Mecklenbrauker I; Saijo K; Malek S N; Desiderio S; Rajewsky K; Tarakhovsky A
AN 2000115868 MEDLINE

L37 ANSWER 14 OF 33 MEDLINE on STN
TI **Redundant** and opposing **functions** of two tyrosine kinases, Btk and Lyn, in mast cell activation.
SO Journal of immunology (Baltimore, Md. : 1950), (2000 Aug 1) 165 (3) 1210-9.
Journal code: 2985117R. ISSN: 0022-1767.
AU Kawakami Y; Kitaura J; Satterthwaite A B; Kato R M; Asai K; Hartman S E; Maeda-Yamamoto M; Lowell C A; Rawlings D J; Witte O N; Kawakami T
AN 2000405288 MEDLINE

L37 ANSWER 15 OF 33 MEDLINE on STN DUPLICATE 10
TI Chimeric constructs containing the SH4/Unique domains of cYes can restrict the ability of Src(527F) to upregulate heme oxygenase-1 expression efficiently.
SO Cellular signalling, (2000 Oct) 12 (9-10) 691-701.
Journal code: 8904683. ISSN: 0898-6568.
AU Hoey J G; Summy J; Flynn D C
AN 2001132356 MEDLINE

L37 ANSWER 16 OF 33 MEDLINE on STN DUPLICATE 11
TI Restoration of thymic development in an Lck(-/-) thymoma overexpressing ZAP-70.
SO Molecular immunology, (2000 Jan-Feb) 37 (1-2) 85-90.
Journal code: 7905289. ISSN: 0161-5890.
AU Ulivieri C; Majolini M B; Baldari C T
AN 2000245601 MEDLINE

L37 ANSWER 17 OF 33 HCAPLUS COPYRIGHT 2005 ACS on STN
TI Restoration of thymic development in an Lck-/- thymoma overexpressing ZAP-70
SO Molecular Immunology (2000), 37(1-2), 59-90
CODEN: MOIMD5; ISSN: 0161-5890
AU Ulivieri, Cristina; Majolini, M. Bernardetta; Baldari, Cosima T.
AN 2000:374577 HCAPLUS
DN 133:134122

L37 ANSWER 18 OF 33 MEDLINE on STN DUPLICATE 12
TI Thyroid hormone receptor-associated proteins and general positive cofactors mediate thyroid hormone receptor function in the absence of the TATA box-binding protein-associated factors of TFIID.
SO Proceedings of the National Academy of Sciences of the United States of America, (1999 Mar 2) 96 (5) 1959-64.
Journal code: 7505876. ISSN: 0027-8424.
AU Fondell J D; Guermah M; Malik S; Roeder R G

AN 1999162540 MEDLINE

L37 ANSWER 19 OF 33 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
TI Specific and **redundant functions** of **Src** and Fyn **kinases** in keratinocyte differentiation control.
SO Journal of Investigative Dermatology, (April, 1999) Vol. 112, No. 4, pp. 564. print.
Meeting Info.: 60th Annual Meeting of the Society for Investigative Dermatology. Chicago, Illinois, USA. May 5-9, 1999.
CODEN: JIDEAE. ISSN: 0022-202X.
AU Cabodi, S. [Reprint author]; Calautti, E.; Stein, P. L.; Dotto, G. P.
AN 1999:264373 BIOSIS

L37 ANSWER 20 OF 33 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN
TI Specific and **redundant functions** of **Src** and Fyn **kinases** in keratinocyte differentiation control
SO JOURNAL OF INVESTIGATIVE DERMATOLOGY, (APR 1999) Vol. 112, No. 4, pp. 247-247.
Publisher: BLACKWELL SCIENCE INC, 350 MAIN ST, MALDEN, MA 02148.
ISSN: 0022-202X.
AU Cabodi S (Reprint); Calautti E; Stein P L; Dotto G P
AN 1999:326723 SCISEARCH

L37 ANSWER 21 OF 33 MEDLINE on STN DUPLICATE 13
TI Drosophila Src42A is a negative regulator of RTK signaling.
SO Developmental biology, (1999 Apr 1) 208 (1) 233-43.
Journal code: 0372762. ISSN: 0012-1606.
AU Lu X; Li Y
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L37 ANSWER 22 OF 33 MEDLINE on STN DUPLICATE 14
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=> d ab 3,6,8,10,11,14-16,19,22-29

L37 ANSWER 3 OF 33 MEDLINE on STN DUPLICATE 2
AB The **Src-family** protein tyrosine **kinases** (SFKs) are known to play key roles in initiating signal transduction by the B-cell antigen receptor (BCR). In addition, numerous studies have shown that this family of molecules also contributes to signaling by BCR surrogates during B-lymphocyte lineage development and maturation. Paradoxically, ablation of SFKs not only results in obvious defects in B-cell development but also in the onset of autoimmunity. Thus SFKs, most notably Lyn, play both activating and inhibitory roles in B-cell function. Confounding analyses of SFK function in B cells is the varied coexpression of family members that mediate **redundant** as well as unique **functions.** In this review, we will focus mainly on the role of Lyn in mediating positive and negative roles in B-cell activation and how these affect immune signaling and disease progression.

L37 ANSWER 6 OF 33 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN
AB While both lck and fyn are essential to generating the full sequelae of proximal signals emanating from the TcR/CD3 complex, thus far, modeling the temporal and spatial involvement of fyn has been problematic. The absence of a binding partner, analogous to the role of CD4 in targeting lck, commonalties of structure, common modes of activation and overlapping substrate specificities support the conclusion that many aspects of their roles may be **redundant.** Whether or how their **functions** are coordinated remains obscure. Recent experiments incorporating membrane partitioning towards resolving the distinct roles of lck and fyn in TcR/CD3 mediated cellular activation demonstrate that the membrane microdomains, termed lipid rafts, function to segregate the two kinases in unstimulated primary cells, and offers resolution in modeling their non-redundant contributions to the proximal TcR/CD3 signaling. Their activation, while interdependent, is temporally and spatially uncoupled. Lck activation is upstream of fyn activation. Moreover lck-dependent fyn activation is unidirectional, predicting the existence of distinct kinase specific regulatory mechanisms operating in lipid rafts. Thus, more than merely vehicles supporting protein concentration, these microdomains provide an environment in which the regulation of enzymatic activities is coupled to and regulated by a temporal coordination of protein translocations subsequent to TcR/CD3/CD4 engagement. (C) 2004 Elsevier Ltd. All rights reserved.

L37 ANSWER 8 OF 33 MEDLINE on STN DUPLICATE 5
AB c-Src-null mutants have not provided a full understanding of the cellular functions of c-Src, reflecting the **functional redundancy** among **Src family** members. c-**Src** is phosphorylated by cyclin-dependent kinase 1 (Cdk1) and Cdk5 at Ser75 in the unique amino terminal c-Src-specific domain. The specific roles of c-Src may be assessed by establishing mouse embryonic stem (ES) cells homozygous for a point mutation at Ser75. Mammalian homozygous cultured cells with a point mutation, however, have not yet been produced by gene targeting. Here we show an efficient procedure for producing ES cell clones bearing a homozygous Ser75 to Asp mutation in the c-src gene. This procedure was developed by combining two previously reported strategies: our procedure for introducing a point mutation into one allele with no exogenous sequence, and the high-geneticin (G418) selection procedure for introducing a mutation into both alleles. The mutant clones expressed the same levels of c-Src protein and autophosphorylation activity as wild-type cells, but the mutant c-Src was not phosphorylated on Ser75 during mitosis. This procedure is feasible for generating cells homozygous for a subtle mutation in most genes, and is expected to be applicable to other

somatic cell lines.

L37 ANSWER 10 OF 33 MEDLINE on STN DUPLICATE 7

AB To identify the physiological role of Hck, a **functionally redundant** member of the **Src family** of tyrosine **kinases** expressed in myelomonocytic cells, we generated Hck(F/F) "knock-in" mice which carry a targeted tyrosine (Y) to phenylalanine (F) substitution of the COOH-terminal, negative regulatory Y(499)-residue in the Hck protein. Unlike their Hck(-/-) "loss-of-function" counterparts, Hck(F/F) "gain-of-function" mice spontaneously acquired a lung pathology characterized by extensive eosinophilic and mononuclear cell infiltration within the lung parenchyma, alveolar airspaces, and around blood vessels, as well as marked epithelial mucus metaplasia in conducting airways. Lungs from Hck(F/F) mice showed areas of mild emphysema and pulmonary fibrosis, which together with inflammation resulted in altered lung function and respiratory distress in aging mice. When challenged transnasally with lipopolysaccharide (LPS), Hck(F/F) mice displayed an exaggerated pulmonary innate immune response, characterized by excessive release of matrix metalloproteinases and tumor necrosis factor (TNF)alpha. Similarly, Hck(F/F) mice were highly sensitive to endotoxemia after systemic administration of LPS, and macrophages and neutrophils derived from Hck(F/F) mice exhibited enhanced effector functions in vitro (e.g., nitric oxide and TNFalpha production, chemotaxis, and degranulation). Based on the demonstrated functional association of Hck with leukocyte integrins, we propose that constitutive activation of Hck may mimic adhesion-dependent priming of leukocytes. Thus, our observations collectively suggest an enhanced innate immune response in Hck(F/F) mice thereby skewing innate immunity from a reversible physiological host defense response to one causing irreversible tissue damage.

L37 ANSWER 11 OF 33 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

AB Erythropoietin receptor (Epo-R) and c-Kit receptor tyrosine kinase play an essential role in blood cell development. Mice lacking the expression of c-Kit or Epo-R die in utero of severe anemia due to impaired erythroid cell proliferation and survival. Previous studies have shown that the functional interaction of Epo-R and c-Kit is essential for normal erythroid cell development (Wu et al., Nature, 1995; Wu et al., PNAS, 1995; Kapur et al., JBC, 2001). However, signaling pathways essential for regulating c-Kit mediated proliferation/survival and cooperation with Epo-R are poorly understood. Activation of c-Kit by its ligand, stem cell factor (SCF) autophosphorylates various cytoplasmic tyrosines (Tyr), which become binding sites for a variety of intracellular signaling molecules, including SH2 domain-containing proteins, Ras-GAP (Tyr 745), PLC-gamma (Tyr 728), PI-3Kinase (Tyr 719), **Src Kinase** (Tyr 567 and 569) and Grb2 (Tyr 702). Whether these diverse signaling pathways induce unique, overlapping, or **redundant functional** outcomes in erythroid cells is unknown. Utilizing an erythroid cell line, and primary fetal liver derived hematopoietic cells expressing eight different mutants of c-Kit in which specific tyrosine (Y) docking residues are replaced by phenylalanine (F), we investigated the functional and biochemical consequences of inactivating the Ras-GAP (Y745F), PLC-gamma (Y728F), PI-3Kinase (Y719F), **Src kinase** (Y567F, Y569F and Y567/569F), Grb2 (Y702F) and all five (Y5F; naked receptor) signaling pathways in c-Kit on proliferation and survival, and on their ability to cooperate with Epo-R. We demonstrate that inactivation of any one of the five signaling pathways in c-Kit, significantly decreases the proliferation and survival of erythroid cells in response to SCF stimulation, although to varying degrees. Most profound decrease in proliferation, survival and erythroid colony forming ability was observed in cells expressing the naked (YF5) c-Kit receptor, followed by c-Kit mutants defective in the activation of Src signaling pathway, including Y567F, Y569F and the double Src mutant Y567/569F. In contrast, cells expressing the c-Kit mutant's that are defective in the activation of

Ras-GAP (Y745F), PI-3Kinase (Y719F), PLC-gamma (Y728F) and Grb2 (Y702F) showed only a modest, but significant decrease in proliferation and survival. Interestingly, when stimulated together with SCF and erythropoietin (Epo), only the naked c-Kit receptor, and the c-Kit mutants defective in the activation of Src signaling pathway showed reduced proliferation, survival and colony forming ability. Further, this decrease was associated with reduced trans-phosphorylation of the Epo-R and c-Myc expression. Restoration of the Src signaling pathway in the naked c-Kit receptor (Y5F) was sufficient to partially restore SCF and Epo mediated cooperation in these cells. These results identify Src signaling pathway as a critical regulator of erythroid cell proliferation and survival downstream from c-Kit and Epo-R. Further, these data shed novel insight into the possible mechanism(s) of cooperation between c-Kit and other growth factor receptors, including Epo-R.

L37 ANSWER 14 OF 33 MEDLINE on STN

AB Protein-tyrosine kinases play crucial roles in mast cell activation through the high-affinity IgE receptor (FcepsilonRI). In this study, we have made the following observations on growth properties and FcepsilonRI-mediated signal transduction of primary cultured mast cells from Btk-, Lyn-, and Btk/Lyn-deficient mice. First, Lyn deficiency partially reversed the survival effect of Btk deficiency. Second, FcepsilonRI-induced degranulation and leukotriene release were almost abrogated in Btk/Lyn doubly deficient mast cells while singly deficient cells exhibited normal responses. Tyrosine phosphorylation of cellular proteins including phospholipases C-gamma1 and C-gamma2 was reduced in Btk/Lyn-deficient mast cells. Accordingly, FcepsilonRI-induced elevation of intracellular Ca2+ concentrations and activation of protein kinase Cs were blunted in the doubly deficient cells. Third, in contrast, Btk and Lyn demonstrated opposing roles in cytokine secretion and mitogen-activated protein kinase activation. Lyn-deficient cells exhibited enhanced secretion of TNF-alpha and IL-2 apparently through the prolonged activation of extracellular signal-related kinases and c-Jun N-terminal kinase. Potentially accounting for this phenomenon and robust degranulation in Lyn-deficient cells, the activities of protein kinase Calpha and protein kinase CbetaII, low at basal levels, were enhanced in these cells. Fourth, cytokine secretion was severely reduced and c-Jun N-terminal kinase activation was completely abrogated in Btk/Lyn-deficient mast cells. The data together demonstrate that Btk and Lyn are involved in mast cell signaling pathways in distinctly different ways, emphasizing that multiple signal outcomes must be evaluated to fully understand the functional interactions of individual signaling components.

L37 ANSWER 15 OF 33 MEDLINE on STN DUPLICATE 10

AB cSrc and cYes are the two most homologous members of the **Src-family** of nonreceptor tyrosine kinases. These kinases perform **redundant** signalling **functions** in cells; however, there is also evidence to support specificity in signalling. In this report, specificity in signalling between activated forms of the cSrc and cYes oncoproteins was examined at the level of downstream gene expression. Here, pp60c-src(527F) (Src(527F)) and chimeric constructs of Src(527F) containing combinations of the SH4/Unique/SH3/SH2 domains of cYes were generated to determine whether the individual modular domains of cSrc or cYes could direct distinct cellular signals leading to differential gene expression. A biased, differential display analysis approach was used to analyse changes in gene expression. The data indicate that Src(527F) is capable of upregulating heme oxygenase-1 (HO-1) in CEF cells at the level of transcription and protein expression. Chimeric constructs containing the SH4/Unique domains of cYes were less efficient in upregulating HO-1 expression. Activation of cSrc and expression of the HO-1 gene product are each induced under conditions of hypoxia. We hypothesize that activated cSrc can direct upregulation of HO-1 while activated cYes may be less efficient in stimulating signal transduction pathways that direct expression of HO-1.

L37 ANSWER 16 OF 33 MEDLINE on STN DUPLICATE 11
AB Thymic development is strictly controlled by **Src** and Syk **family** protein tyrosine kinases. The major players in this process are Lck and ZAP-70, which regulate critical differentiation steps of thymopoiesis. Notwithstanding the critical role of Lck and ZAP-70 in thymocyte development as compared to the related kinases Fyn and Syk, a partial **functional redundancy** between members of the same family of protein tyrosine kinases has emerged from studies on genetically manipulated mouse models. Furthermore, a close functional interplay between Lck and ZAP-70 in intracellular signaling has been shown to occur in thymocytes. Here we present the characterization of a thymoma from an Lck(-/-) mouse, where the block in thymocyte development is overcome and the transition between the CD4(-)CD8(-) and CD4(+)CD8(+) stages is fully restored. Determination of the expression levels of Fyn, ZAP-70 and Syk in thymocytes form the Lck(-/-) thymoma revealed high levels of ZAP-70 overexpression and recovery of a specific subset of phosphoproteins as compared to Lck(-/-) thymocytes. Hence ZAP-70 overexpression in thymocytes is associated with recovery from the developmental arrest caused by the absence of Lck, suggesting a role for ZAP-70 downstream of Lck in the maturation of CD4(+)CD8(+) thymocytes.

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L37 ANSWER 22 OF 33 MEDLINE on STN DUPLICATE 14
AB By using antisense RNA, Lck-deficient transfectants of a T helper 2 (Th2) clone have been derived and shown to have a qualitative defect in the T cell receptor signaling pathway. A striking feature observed only in Lck-deficient T cells was the presence of a constitutively tyrosine-phosphorylated 32-kDa protein. In the present study, we provide evidence that this aberrantly hyperphosphorylated protein is p34(cdc2) (cdc2) a key regulator of cell-cycle progression. Lck-deficient transfectants expressed high levels of cdc2 protein and its regulatory units, cyclins A and B. The majority of cdc2, however, was tyrosine-phosphorylated and therefore enzymatically inactive. The transfectants were significantly larger than the parental cells and contained 4N DNA. These results establish that a deficiency in Lck leads to a cell-cycle arrest in G2. Moreover, transfected cells were hypersusceptible to apoptosis when activated through the T cell receptor. Importantly, however, this hypersusceptibility was largely reversed in the presence of T cell growth factors. These findings provide evidence that, in mature T lymphocytes, cell-cycle progression through the G2-M check point requires expression of the **Src-family** protein tyrosine **kinase**, Lck. This requirement is Lck-specific; it is observed under conditions in which the closely related Fyn kinase is expressed normally, evincing against a **redundancy** of **function** between these two kinases.

L37 ANSWER 23 OF 33 MEDLINE on STN DUPLICATE 15
AB The **Src family** protein tyrosine **kinases** (PTKs), Lck and Fyn, are coexpressed in T cells and perform crucial functions involved in the initiation of T cell antigen receptor (TCR) signal transduction. However, the mechanisms by which Lck and Fyn regulate TCR signaling are still not completely understood. One important question is whether Lck and Fyn have specific targets or only provide **functional redundancy** during TCR signaling. We have previously shown that Lck plays a major role in the tyrosine phosphorylation of the TCR-zeta chain and the ZAP-70 PTK. In an effort to identify the targets that are specifically regulated by Fyn, we have studied the tyrosine phosphorylation of Pyk2, a recently discovered new member of the focal adhesion kinase family PTK. We demonstrated that Pyk2 was rapidly tyrosine phosphorylated following TCR stimulation. TCR-induced tyrosine phosphorylation of Pyk2 was selectively dependent on

Fyn but not Lck. Moreover, in heterologous COS-7 cells, coexpression of Pyk2 with Fyn but not Lck resulted in substantial increases in Pyk2 tyrosine phosphorylation. The selective regulation of Pyk2 tyrosine phosphorylation by Fyn in vivo correlated with the preferential phosphorylation of Pyk2 by Fyn in vitro. Our results demonstrate that Pyk2 is a specific target regulated by Fyn during TCR signaling.

L37 ANSWER 24 OF 33 MEDLINE on STN DUPLICATE 16
AB **Src family** protein tyrosine **kinases** are activated following engagement of many different classes of cellular receptors and participate in signaling pathways that control a diverse spectrum of receptor-induced biological activities. While several of these kinases have evolved to play distinct roles in specific receptor pathways, there is considerable **redundancy** in the **functions** of these kinases, both with respect to the receptor pathways that activate these kinases and the downstream effectors that mediate their biological activities. This chapter reviews the evidence implicating **Src family kinases** in specific receptor pathways and describes the mechanisms leading to their activation, the targets that interact with these kinases, and the biological events that they regulate.

L37 ANSWER 25 OF 33 MEDLINE on STN
AB Non-receptor tyrosine kinase Chk has been implicated in hematopoietic development. To study the function of Chk in vivo, we have generated chk-deficient mice using gene targeting. Overall development of mice homozygous for this mutation was apparently normal. Blood counts, FACS analysis of hematopoietic cell populations, CFU-C and CAFC assays showed no significant difference between wild type and mutant animals. Thus, the dispensability of Chk for mouse development and hematopoiesis suggests that its **function** may be **redundant** in vivo, and most likely be compensated by activity of a closely related protein tyrosine kinase Csk.

L37 ANSWER 26 OF 33 MEDLINE on STN DUPLICATE 17
AB Two families of protein tyrosine **kinases** (PTKs), the **Src** and Syk/ZAP-70 families, are required for T cell development. Lck is the major **Src family** member required for thymopoiesis, since there is a severe deficit of CD4+CD8+ thymocytes and mature T cells in its absence. However, some peripheral T cells are evident in these mice, suggesting that additional PTKs may contribute to T cell development. Here we show that the combined disruption of Lck and Fyn (lck(-/-)fyn(-/-)) completely arrests alpha beta T cell development at the CD4-CD8- stage. The development of V gamma 3+ dendritic epidermal T cells is also severely impaired, but natural killer cell development and cytolytic activity is unaffected in lck(-/-)fyn(-/-) mice. These findings reveal the potential for **redundant functions** mediated by **Src family** PTKs while emphasizing crucial roles for Lck and Fyn in T cell development.

L37 ANSWER 27 OF 33 MEDLINE on STN DUPLICATE 18
AB p59fyn is one of the **Src-family kinases** thought to play an important role in signaling through T cell receptor. However, Fyn deficiency has caused no overt defects in vivo on T cell development, nor has it caused any changes in the phosphorylation status of molecules such as ZAP-70 which have been proposed as p59fyn substrates. This could be explained as being due to compensation of Fyn deficiency by other **Src-family kinases.** Here, we have 'knocked-in' the csk gene, a negative regulator of **Src-family kinases**, into fyn locus to challenge the problem of **redundant functions** among **Src-family kinases.** The csk-'knock-in' mice displayed atrophy of the thymic cortex and impaired development of CD4+ CD8+ thymocytes. This was concomitant with decrease in tyrosine

phosphorylation of ZAP-70 and p120cbl.

L37 ANSWER 28 OF 33 MEDLINE on STN DUPLICATE 19
AB The protein tyrosine **kinase** c-**Src** is transiently activated at the transition from the G2 phase to mitosis in the cell cycle of mammalian fibroblasts. Fyn and Yes, the other members of the **Src family** present in fibroblasts, were also found to be activated at mitosis. In cells microinjected with a neutralizing antibody specific for Src, Fyn, and Yes (anti-cst.1) during G2, cell division was inhibited by 75 percent. The block occurred before nuclear envelope breakdown. Antibodies specific for phosphatidylinositol-3 kinase alpha and phospholipase C-gamma 1 had no effect. Microinjection of the Src homology 2 (SH2) domain of Fyn was also inhibitory. **Functional redundancy** between members of the **Src family** was observed; a **Src**-specific antibody had no effect in NIH 3T3 cells but inhibited cell division in fibroblasts in which the only functional **Src family kinase** was **Src** itself. Thus, **Src family kinases** and proteins associating with their SH2 domains are required for entry into mitosis.

L37 ANSWER 29 OF 33 MEDLINE on STN DUPLICATE 20
AB The antigen receptor of B lymphocytes (BCR) plays important roles in recognition of foreign antigens and self-components to allow the immune system to make appropriate antibody responses. The BCR is a complex between membrane immunoglobulin and the Ig-alpha and Ig-beta heterodimer. Site-directed mutagenesis experiments have shown that the mu heavy chain transmembrane domain plays a key role in the association of mIgM with Ig-alpha/Ig-beta. In the absence of complex formation, mIgM is retained in the endoplasmic reticulum, and this function is also specified by the mu chain transmembrane domain. The ability of various mutant mIgM molecules to associate with Ig-alpha/Ig-beta correlates well with their ability to induce signal transduction reactions such as protein tyrosine phosphorylation and phosphoinositide breakdown. Thus, the signaling ability of the BCR appears to reside in the Ig-alpha/Ig-beta heterodimer. The cytoplasmic domains of Ig-alpha and Ig-beta each contain an ITAM sequence, which is defined by its limited homology with subunits of the T-cell antigen receptor and of Fc receptors. Moreover, chimeric proteins containing these ITAMs and surrounding sequences from the cytoplasmic domains of Ig-alpha or Ig-beta exhibit signaling function characteristics of the intact BCR. The Ig-alpha and Ig-beta chimeras are each capable of inducing all of the BCR signaling events tested and thus represent **redundant functions.** Cross-linking these chimeras leads to their phosphorylation and to binding of the intracellular tyrosine kinases Lyn and Syk. The BCR expressed in the nonlymphoid AtT20 cells, which express the **Src-family** tyrosine **kinase** Fyn but not Syk, was not able to trigger vigorous signaling reactions. Introduction of the active form of Syk into these cells restored some signaling events. These results are consistent with a model in which the ITAMs act to initiate the BCR signaling reactions by binding and activating tyrosine kinases.

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